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The impact of prophylactic percutaneous endoscopic gastrostomy (PEG) in head and neck cancer patients treated with radiotherapy

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Abstract
Aim: The purpose of this study is to compare the patients with head and neck cancer (HNC) who underwent radiotherapy (RT) with or without prophylactic percutaneous endoscopic gastrostomy (PEG) in terms of weight loss, interruption of treatment, and survival.
Material and Methods: The data of 64 patients who were diagnosed with HNC and received RT in our clinic between November 2013 and July 2019 were evaluated retrospectively. Only cases with prophylactic PEG were included. Patients in the negative PEG (nPEG) (n:43) and positive PEG (pPEG) (n:21) arms are similar apart from the primary subsite.
Results: The median follow-up time was 20 months (range 2- 62 months). The 20-month OS was 76.3% and 58.8% for nPEG and pPEG patients, respectively (p=0.05). Weight loss after RT was higher in the nPEG arm compared to the pPEG arm, but not statistically significant (p=0.18). No significant differences were observed in terms of acute and late adverse effects. There was no significant difference between the duration of RT interruption in patients and the PEG status (p=0.53).
Discussion: No significant effect of the nutritional status by prophylactic PEG on weight loss, treatment interruption and oncological outcomes in patients with HNC who underwent RT has been demonstrated. However, well designed, larger studies are needed comparing patients with and without prophylactic enteral tube placement.

Keywords
Prophylactic PEG; Nutrition; Head and neck cancer; Chemoradiotherapy; Survival

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Introduction

Chemoradiotherapy (CRT) is an effective treatment option in the definitive treatment for locally advanced head and neck cancer (HNC). It is pleasing that CRT not only allows organ protection but also improves the disease and provides a complete cure. However, serious acute and late toxicity remains an important problem despite developing technology and advanced radiotherapy techniques [1, 2]. In most patients with HNC, there is a deterioration in nutrition and quality of life due to acute adverse effects such as mucositis, dysphagia, and odynophagia. In the oropharynx and oral cavity tumors, due to tumor-related swallowing difficulties, nutritional disorders and malnutrition are observed [3-6]. As a result, all this can lead to discontinuation of the treatment, which adversely affects disease control. It is undesirable because radiobiologically, interruption of radiotherapy (RT) in patients with HNC will cause the re-population of tumoral cells. It is predicted that the tumor control rate of HNC decreases by at least 1% by taking a break to RT for each day [7-10]. In the literature, it has been reported that pre-treatment nutritional status predicts response to therapy and even survival [11].

Enteral tube placement is used to support nutrition in patients with HNC who received CRT, which is most preferred the ease of use of percutaneous endoscopic gastrostomy (PEG) [12]. In which part of the treatment PEG should be placed in patients with HNC, this issue is not clear in the literature. Unfortunately, there is no consensus as to whether PEG should be placed before treatment (prophylactic PEG) or in case of clinical necessity after treatment has started [13-16]. There are undesirable conditions caused by the utilize of PEG, such as PEG-associated dysphagia and long-term PEG dependence [17].

We also placed prophylactic PEG before RT in order to avoid interrupting treatment for some of the patients with HNC, selected according to clinician experience. The purpose of this study is to compare the patients of HNC who underwent RT with or without PEG in terms of weight loss, interruption of treatment, and survival. There is an opinion in the literature that reactive PEG (i.e. in case of nutritional support necessity) should be preferred instead of prophylactic PEG [12-16]. In this study, the results of our patients with HNC who had prophylactic PEG were compared with these studies in the literature. Furthermore comparing patients with and without PEG in terms of survival makes our study important.

Material and Methods

The data of 64 HNC patients who received RT in Tokat Gaziosmanpaşa University Radiation Oncology Clinic between November 2013 and July 2019 were evaluated retrospectively. The Departmental Ethics Committee of Tokat Gaziosmanpaşa University's Faculty of Medicine on non-invasive clinical research approved this trial in accordance with the Declaration of Helsinki with the decision no 2020/04, on 5 March 2020. Patient interview information, patient files, and electronic system data were used for the study. The patients' demographic status, diagnosis dates, hematological results, PEG status, treatment details, weight follow-up during RT, adverse effect status, responses to treatment, and their last status were noted. There is no reactive PEG in our study. It was decided to insert prophylactic PEG especially for patients who had swallowing problems due tumor localization. Weekly weight measurements were recorded just before the start of RT and during RT. The follow-up, training for using PEG and calorie calculation of patients with prophylactic PEG was performed by the same nurse.

The primary endpoint is the relationship between treatment-related weight loss, treatment interruption, and PEG status. The secondary endpoints of the study are overall survival (OS), progression- free survival (PFS). The date of diagnosis is considered as the onset date for OS and PFS. The endpoint for the OS is the last control date for the patients living and the exitus date for exitus ones. The endpoint for PFS is the first event date for patients with recurrence and distant metastasis, and the last control date for patients without relapse and metastasis. Adult patients with pathological evidence of HNC with full access to knowledge were included in the study. Patients with missing files and follow-up information were excluded.

Statistical analysis

The data were calculated using SPSS version 24. Descriptive statistics for continuous (quantitative) variables were expressed as mean, standard deviation, minimum and maximum values and for categorical variables, as number (n) and ratio (%). Nonparametric tests were used as the variables are not suitable for normal distribution. The categorical demographic characteristics of the patients were calculated with the Chi-square and Fisher's exact test. Spearman's rank correlation test was utilized for univariate correlation analysis. The Mann-Whitney U test was performed for two groups of independent statistical analysis, and the Kruskall-Wallis test for 3 or more independent group analyzes. After Bonferroni correction, significance was assessed by post-hoc analysis. Kaplan-Meier test was employed for survival analysis and the log-rank test for comparison. In multivariate analysis, the Cox regression test was applied. Statistical significance was admitted as less than 0.05.

Results

Demographic data, treatment details of patients are summarized in Table 1. Twenty-one patients in the positive PEG arm and 43 patients in the negative PEG arm were studied. Patients in the negative PEG (nPEG) and positive PEG (pPEG) arms were similar in terms of median age, gender, operational status, comorbid disease, stage, RT details and chemotherapy (CT), and there was no significant difference between the two groups (Table 1). Apart from the primary subsite, nPEG and pPEG groups were similar. In the nPEG arm, the diagnosis of nasopharyngeal carcinoma was significantly higher, in the pPEG arm, oral cavity and oropharyngeal cancer were higher.

The relationship between survival and PEG status

The median follow-up time was 20 months (range 2- 62 months). The 20-month OS was 76.3% and 58.8% for nPEG and pPEG patients, respectively (p=0.05). The 20-month PFS was 67.8% and 50.8% for nPEG and pPEG patients, respectively (p=0.02) (Figure 1). In the 20-month follow-up period, the use of PEG significantly negatively affected the oncological results

Table 1. Patients Demographics and Treatment Details

		nPEG	pPEG	p
Age	Median (Range)	59 (34-85)	59 (37-88)	0.90
Gender	Male /Female (n)	36/7	15/6	0.34
Surgery	No	31 (72.1%)	16 (76.2%)	0.48
	Yes	12 (27.9%)	5 (23.8%)	
Primary Subsite	Nasopharynx	39 (90.7%)	9 (42.9%)	**0.001**
	Hypopharynx	1 (2.3%)	5(23.8%)	
	Oral Cavity	2 (4.7%)	5(23.8%)	
	Unknown Primary	1(2.3%)	0	
Comorbidity	Unknown	2 (4.7 %)	1 (4.8%)	0.26
	Presence	17 (39.5%)	10(47.6%)	
	Absence	24(55.8%)	10 (47.6%)	
Pathology	SCC	33 (76.7%)	15 (71.4%)	0.64
	Nonkeratinized	4 (9.3%)	4 (19%)	
	Undifferentiated	5(11.6%)	2 (9.5%)	
	Adenocarcinoma	1 (2.3%)	0	
Clinical T	cT_1	12 (27.9%)	5(23.8%)	0.57
	cT_2	6 (14%)	4 (19%)	
	cT_3	18 (41.9%)	6(28.6%)	
	cT_4	7 (16.3%)	6 (28.6%)	
Clinical N	cN_0	22 (51.1%)	8 (38%)	0.42
	cN_1	3 (6.9%)	3 (14.2%)	
	cN_2	17 (39.5%)	10 (47.8%)	
	cN_3	1(2.5%)	0	
Metastasis	M_0	41 (95.3%)	21 (100%)	0.44
	M_1	2 (4.7%)	0	
RT tecnnique	IMRT	42 (97.7%)	21 (100%)	0.67
	No IMRT	1(2.3%)	0	
Concomitant CT	No	15 (34.9%)	3(14.3%)	0.074
	Yes	28 (65.1%)	18 (85.7%)	
Induction CT	No	38 (88.4%)	19(90.5%)	0.58
	Yes	5(11.6%)	2 (9.5%)	

Abbreviations: SCC: Squamous cell carcinoma; IMRT: Intensity-modulated radiotherapy; CT: Chemotherapy; pPEG: positive PEG; nPEG: negative PEG

Table 2. The relationship between PEG and recurrence

	Local recurrence	Distant recurrence	Local + distant recurrence	p
nPEG	2 (%28.3)	4(%57.1)	1(%14.3)	0.073
pPEG	8(%72.7)	1 (%9.1)	2 (%18.2)	

Abbreviations: pPEG: positive PEG; nPEG: negative PEG

of the patients.

Higher local recurrence was shown in patients with PEG, but not statistically significant (p0.073) (Table 2).

The relationship between weight loss-treatment interruption and PEG status

The main goal of prophylactic PEG implantation is the patients' concern for weight loss / malnutrition [18]. For this purpose, the weekly weight values of our patients were recorded before and during the treatment. The percentage value of weight loss in body weight was calculated. The duration of treatment interruptions was examined.

The median weight values of our patients before RT were similar in the nPEG and pPEG arms. Weight loss after treatment was higher in the nPEG arm compared to the pPEG arm (6.9% (0-23.5) vs 4.3% (1.3-11.5)), but the difference was not statistically significant (p=0.18) (Table 3).

Table 3. The evaluation of the relationship between PEG and variables

		nPEG	pPEG	p
PreRT weight	Median (Range)(Kg)	74 (47-124)	71 (47-80)	0.10
PostRT weight	Median (Range)(Kg)	72 (44-109)	66.5 (44-79)	0.074
Weight loss	Median (Range)(%)	6.9% (0-23.5)	4.3% (1.3-11.5)	0.18
Treatment Gap	Median (Range)(Day)	1 (0-14)	1 (0-12)	0.53
Acute adverse effect	No	31 (72.1%)	10 (47.6%)	0.052
	Yes	12 (27.9%)	11(52.4%)	
Acute adverse effect details	Gr1 RD	2 (16.7%)	0	0.34
	Gr2 RD	0	1 (9.1%)	
	Gr2 mucositis/dysphagia	8 (66.7%)	9 (81.8%)	
	Gr3 mucositis/dysphagia	2 (16.7%))	1 (9.1%)	
Late adverse effect	No	42 (97.7%)	20 (95.2)	0.55
	Yes	1 (2.3%)	1(4.8%)	
Time until the start of RT	Median (Range)(Day)	92 (27-835)	95 (66-226)	0.86

Abbreviations: pPEG: positive PEG; nPEG: negative PEG; RT: Radiotherapy; Gr: Grade; RD: Radiodermatitis

When the relationship between the duration of RT interruption in patients and PEG status was analyzed, no statistically significant difference was observed between the two groups (p=0.53) (Table 3) (Figure 2).

The relationship between acute and late adverse effects and PEG status

Acute adverse effects were observed in 12 (27.9%) patients in the nPEG arm and in 11 (52.4%) patients in the pPEG arm (0.052). The difference was close to the limit of significance. No significant differences were observed in terms of the details of acute adverse effects (grade, radiodermatitis or mucositis) (p=0.34) (Table 2). Grade 3 dysphagia was higher in the nPEG arm (2 (16.7%) vs 1 (9.1%) patient) (p=0.53).

There was no significant difference with respect to late adverse effects between the two groups (p=0.55).

Discussion

In the present study, the effect of utilization of prophylactic PEG between two homogeneous groups in respect of adverse effects and long-term oncological results was evaluated. The most striking result of our study is that OS and PFS were adversely affected in patients with PEG. The 20-month OS was 76.3% and 58.8% for nPEG and pPEG patients, respectively (p=0.05). The 20-month PFS was 67.8% and 50.8% for nPEG and pPEG patients, respectively (p=0.02). In the 20-month follow-up period, the use of PEG significantly negatively affected the oncological outcomes of the patients. The median weight values of our patients before RT were similar between the two groups. Weight loss after RT was higher in the nPEG arm compared to the pPEG arm, but not statistically significant (p=0.18). No significant differences were observed in terms of acute and late adverse effects. When the relationship between patients' duration of RT interruption and PEG status was

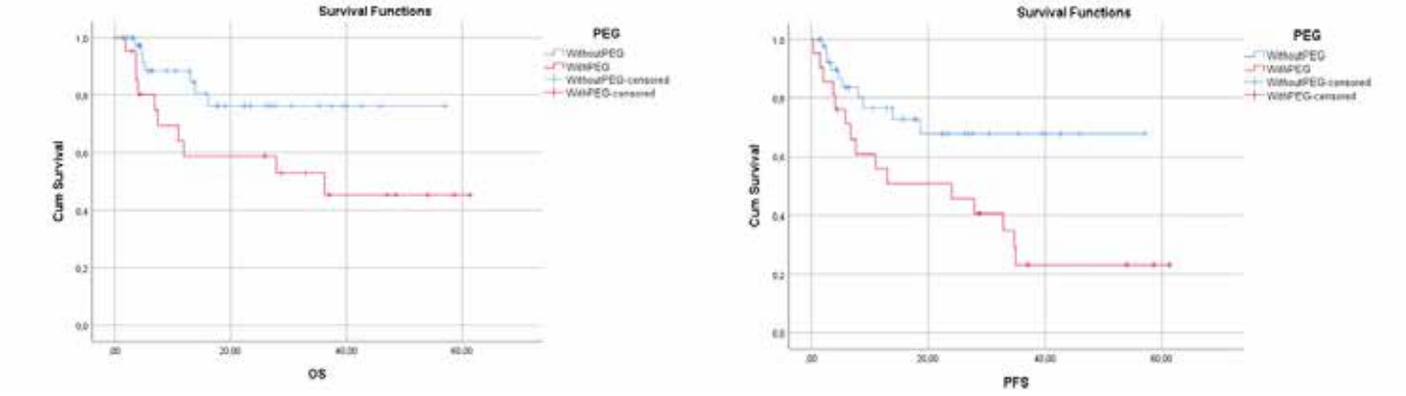

Figure 1. Significantly higher OS and PFS were observed in nPEG patients

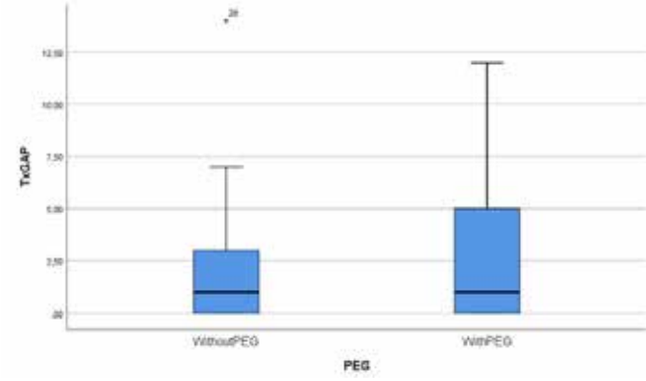

Figure 2. There is no significant correlation between PEG status and duration of RT interruption (p=0.53)

analyzed, no statistically significant difference was observed between the two groups (p=0.53). In summary, less weight loss was observed in patients using PEG, but the difference was not significant. However, this did not change the oncological results and did not improve survival and local recurrences.

In a review, researchers investigated the results of prophylactic PEG (pPEG) and reactive PEG (rPEG) use in HNC patients undergoing CRT using 22 studies [17]. They reported that pPEG reduced the number of malnourished patients, but the mean weight loss measured at different time points was similar for pPEG and rPEG. Prophylactic PEG improved the quality of life of patients in the first 6 months but increased long-term PEG dependence. According to this review, pPEG should be placed in patients who appear to have a high risk of developing malnutrition during treatment [17]. Similarly, in our study, prophylactic PEG placement could not be illustrated as an advantage with respect to interrupting treatment, adverse effects, or oncological outcomes.

Yang et al. [19] retrospectively assessed 192 HNC patients with regard to PEG usage. Although 63% (121) of patients had prophylactic PEG, 80% of them provided actual use. Pretreatment KPS > 80, no pretreatment dysphagia, no concomitant chemotherapy and gabapentin use were associated with reduced PEG usage. Patients who will be placed prophylactic PEG should be chosen well [19]. In another similar study, it was reported that prophylactic PEG may be indicated in the presence of nodal disease and if bilateral neck irradiation will be performed [20].

Nutritional support has been shown to reduce weight loss, hospitalization and RT interruption [6, 21]. Although this group of patients was thought to have received effective treatment and therefore had better oncological results, survival was significantly lower in the prophylactic PEG group in our study. The reason for this situation may be that the time from diagnosis to the start of treatment (minimum value) is 55 days in the negative PEG arm and 66 days in the prophylactic PEG arm. In other words, patients with prophylactic PEG could not start treatment earlier than 2 month. We believe that a significantly lower survival in the pPEG arm may be associated with prolonged time to onset of treatment. Another remarkable situation was that there was no difference between the two arms in all other aspects, whereas primary subsite nasopharynx tumor was more in the nPEG arm, and hypopharynx-oral cavity tumors, which have a poor prognosis, were more in the pPEG arm. Similarly, higher recurrence in the pPEG arm had a negative effect on survival. Based on all this, we thought that survival was reduced in the pPEG arm.

In one of the centers in Germany, 53 patients with hypopharynx Ca who underwent induction CT and CRT were investigated in respect of nutritional status and its effect on clinical outcomes [22]. Prophylactic PEG was not placed at the start of treatment. Seventeen of the 53 patients required enteral feeding during therapy. Similar to our study, nutritional status had no effect on overall survival, recurrence-free survival and treatment-related toxicity [22]. In another study [13], the authors compared prophylactic and reactive PEG in 74 patients with HNC who underwent CRT. The patients were exactly matched in terms of age, gender, TNM stage, tumor subsite, HPV status, and RT dose. There was no difference between the two groups with respect to weight loss, survival and disease control [13]. Prophylactic PEG has been shown to be associated with worse quality of life after RT, more PEG dependence and complications [13-17]. In accordance with the literature, we could not demonstrate a positive effect of prophylactic PEG on weight loss, treatment-related toxicity, and oncological results in our study.

In their study, Silender et al. [23] randomized 134 HNC patients to either prophylactic PEG or nutritional care arms, for comparing weight loss, quality of life and dysphagia. There was no significant difference in weight loss in the first six months. The reason why weight loss is similar in both arms was that treatment-related dysphagia was further in the first six months [23]. We found more acute adverse effects in the pPEG arm, but

grade 3 dysphagia was higher in the nPEG arm (2 (16.7%) vs 1 (9.1%) patients) (p=0.53).

The weak point of the study was that the patients did not fill any quality of life form (EORTC QLQ-H & N35 Swallowing Scale, etc.), and the analyzes were made according to the clinician observation notes. Also, side effects, especially PEG-related dysphagia, could not be evaluated due to missing notes in the file. The strengths of our study are the assessment of PEG between two homogeneous groups, and despite the lack of OS and PFS evaluation in many studies, our study also provides data on this issue.

Conclusion

Consequently, no significant effect of the nutritional status by prophylactic PEG on weight loss, treatment interruption and oncological outcomes in patients with HNC who underwent chemoradiotherapy has been demonstrated. However, well designed, larger studies are needed comparing patients with and without prophylactic enteral tube placement.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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